

REMARKS

The courtesy of the Examiners Dr. Khalid Masood and Dr. James Housel in granting an Interview on this application to the applicant's representative, Mr. Michael Stewart, and to the Director of Industrial Property of Assignee, Dr. Gavin Zealey, is such appreciated. It is believed that the Interview was material in advancing the prosecution of this application. The remarks made herein complement and supplement those made to the Examiner at the Interview.

A clerical error has been corrected in claim 5.

The Examiner objected to the specification under 35 USC 112, first paragraph, as failing to provide an adequate written description.

In particular, the Examiner objected that the meaning the term "non-infectious and immunogenic RS virus", as used in claim 1, and "purified inactivated RS", as used in claim 5 when using non-ionic detergents was not clear. However, applicants had amended claims 1 and 5 to refer to "viral preparation". The Examiner noted this change but indicated that the change failed to overcome the objection, wherein further explanation as to why applicants modification was considered unsatisfactory.

This matter was discussed at the Interview. As reflected in the Interview Summary Record, applicants viral preparation contains the whole purified virus although not necessarily intact. The detergent-inactivated preparation is a split virus.

Having regard to the language employed and the explanation contained herein, it is submitted that the specification is not open to objection under 35 USC 112, first paragraph, as failing to provide an adequate written description in this respect.

The Examiner comments in the Office Action that:

"Applicants further argue that an objection to the specification and rejections under 35 USC 112, first paragraph, is nothing more than lack of utility under 35 USC 101 of copending application 08/472,174. Since claims 1 to 16 are limited to this application and not to the copending

application therefore, lack of utility under 35 USC 101 has been considered in the instant application."

As pointed out at the Interview, this statement arises from a misinterpretation of applicants comments.

Applicants comments on page 4 of the Amendment of April 4, 1996 referred to "the parent application" i.e. Application No. 08/102,743 and not 08/472,174 (a divisional of this application). In that application, i.e. Application No. 08/102,742, the Examiner rejected the claims under 35 USC 101 as lacking patentable utility, stating:

"Because of the shortcomings of the cotton rat as an animal model for RSV as discussed above, it is not possible to extrapolated to effectiveness of the vaccine from results of the cotton rat model to the effectiveness of the vaccine in human."

The Examiner is correct that no rejection of the claims as lacking utility has been made in this application under 35 USC 101. However, the language used to justify objection to the specification under 35 USC 112, first paragraph, is almost identical to that used to justify rejection under 35 USC 101 in the parent case and withdrawn in this application (i.e. no rejection has made in this filing). As stated in the prior Office Action of October 5, 1995 and in the outstanding Office Action, the Examiner states:

"... protection observed in the cotton rat model cannot be extrapolated to humans. Due to the unpredictability of RSV vaccines to provide protection in humans, it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans."

It is clear from this quotation that the Examiner considers the vaccine to lack of utility in humans. Rejections of utility are made under 35 USC 101 and are governed by the Office Guidelines on Utility. It is again noted that the rejection made under 35 USC 101 in the parent application was not repeated in this filing. However, the Examiner cannot use 35 USC 112, first paragraph, as the basis for, what is in effect, a disguised rejection under 35 USC 101, which, it is submitted, is what the Examiner is doing here.

In any event, the issue of whether or not the cotton rat is a model of human efficacy for infection by RSV was discussed in detail in the Amendment of April 4, 1996, particularly on pages 5 to 9. In the Office Action the Examiner states:

"Applicants arguments have been considered in this context but are not deemed to be persuasive."

However, the Examiner does not explain in what respect applicants arguments are not considered persuasive. As discussed at the Interview, it is impossible for applicants to argue the Examiner's position in the absence of any such explanation.

The applicants hereby incorporate by reference the remarks made on pages 5 to 9 of the Amendment of April 4, 1996 and the references referred to therein with respect to the art recognition of the cotton rat animal model, it is particularly pointed out the Murphy et al in WO 93/21310 specifically states:

"....it would appear that the cotton rat constitutes as relevant model for precluding success of an RSV vaccine in infants and small children." (page 10, lines 16 to 18).

The Examiner's attention also is directed to the whole passage running from page 9, line 21 to page 10, line 21 of WO 93/21310.

The first named inventor on this patent publication is a world-recognized expert on RSV vaccines. Accordingly, it is quite clear that those skilled in the art consider the cotton rat to be the relevant model for predicting the success of a RSV vaccine in infants and small children. Accordingly, applicants data, which shown protection of cotton rats immunized with applicants preparations, when exposed to live virus, can be extrapolated to protection in humans. The manner of determining effective doses and mode and frequency of administration of the vaccine to humans are well within the routine skill of the art to determine. There is no undue experimentation involved.

As indicated in the Interview Summary Record, the Examiner agreed to reconsider the objection to the

specification under 35 USC 112, first paragraph and the comparison rejection of claims 1 to 4 and 15 to 16 under 35 USC 112, first paragraph, for the reasons set forth in the objection to the specification, in this respect.

The Examiner further objected to the specification under 35 USC 112, first paragraph on the basis that:

"... it would not be unexpected that BPL or ascorbic acid could similarly modify the RSV F surface glycoprotein and result in potentiation of disease such as was observed with formalin."

As was pointed out to the Examiner at the Interview, it has been stated on the record:

"... in applicants experiments, no evidence of the enhanced pulmonary pathology with either the BPL inactivated vaccine or the ascorbic acid activated vaccine exists" (Emphasis added - see page 10 of Amendment of April 4, 1996, first paragraph).

There is no indication in the Office Action why this statement of fact by the applicant is insufficient to overcome this ground of objection. It is noted that statements made on the record for the purposes of deceiving the Examiner as to the true state of affairs constitute inequitable conduct, sufficient to render any granted patent unenforceable.

Clearly, applicants are not going to make untrue statements on the record and such statements must be accepted by the Examiner as a statement of the facts as they exist. The Examiner does not explain in the Office Action why applicants assurances in this respect are inadequate.

The Examiner further states:

".... it is not predictable [that] other non-ionic detergents would have the same effect on the RSV glycoproteins as octylglucopyranoside and whether the results of inactivation with other non-ionic detergents would be the same as octylglucopyranoside in terms of pulmonary pathogenicity."

It was conceded at the Interview the applicants have specific data showing lack of disease potentiation with the OG-inactivated RSV vaccine (Table 1).

As discussed in more detail at the Interview and discussed in the Amendment of April 4, 1995, on page 10 and again on page 12, as well as in the introductory portion of

the specification, for many years the production of an RS virus vaccine has been hampered by the adverse effects produced with a formalin-inactivated RS virus in a human clinical trial conducted in the United States in the 1960's. In view of these results, the efforts of vaccine producers in the last 30 years have concentrated on the production of live attenuated RS virus mutants or subunit vaccines, rather than the use of inactivation. As drawn to the Examiner's attention in the April 4 Amendment, various review articles relating to the RS virus quite clearly demonstrate that no consideration is being given by the art to the inactivation of virus for providing an RS virus vaccine. There is a clear prejudice in the art against using such procedure.

The applicants have found that, if the virus first is purified and then inactivated using BPL, ascorbic acid or OG, then a safe and effective vaccine preparation can be obtained which, in particular, elicits protective immune response without causing enhanced pulmonary pathology.

It is noted that the three materials used and exemplified act in quite different manners to achieve inactivation of the virus. In this regard, it is noted  $\beta$ -propiolactone modifies nucleic acid bases, mainly purines and most preferably guanine, of the viral genome and blocks its replication (see Budowsky et al, 1993, Vaccine 11(3):343-348). Ascorbic acid is reducing agent and may involve single strand breaks in the DNA molecule, leading to loss of infectivity (see Salo et al, 1978, App. Env. Microbiol 36:68-75) and may also affect virus replication (see Bissell et al, 1980, PNAS USA, 77:2711-2715). n-octyl- $\beta$ -D-glucopyranoside acts as a non-ionic detergent which disrupts the viral envelope inactivating the virus. Copies of the above-cited references are enclosed and listed on the attached PTO-1449.

Having regard to the applicants key finding that enhanced pulmonary pathology can be avoided by first purifying the virus and then inactivating the virus, it is submitted that it is reasonable extrapolation of the results obtained

with OG to extend the scope to other non-ionic detergents which are able to inactivate the virus.

Accordingly, it is submitted that the specification is not open to objection under 35 USC 112, first paragraph in these respects and, hence, the objection and corresponding rejection of claims 1 to 7, 9 and 10 to 16 under 35 USC 112, first paragraph, for the reasons of objection to the specification, should be withdrawn.

The Examiner rejected claims 1 to 4, 15 and 16 under 35 USC 103 as being unpatentable over Bordt et al in view of Downing et al and further in view of McIntosh et al.

These claims relate to the inactivated RS viral preparation. The innate prejudice in the art against inactivation of virus as a viable route to the production of safe and effective RSV vaccine has been described above and is evident from the materials previously submitted.

As the Examiner corrected points out:

"Bordt et al teach a bovine respiratory syncytial virus which is inactivated with ascorbic acid.... Downing teach a method of preparing respiratory syncytial virus (RSV) ... to produce a virus substantially free from cellular and serum components.... McIntosh teach that human respiratory syncytial virus is the most important cause of viral lower respiratory tract disease in infants and children and that human RSV is a paramyxovirus."

However, nowhere does this prior art suggest inactivation of purified virus as required by applicants claims. While it is true that the Bordt et al reference discloses a bovine respiratory syncytial virus inactivated with ascorbic acid, as stated by the Examiner, nevertheless, it is also clear from the description in Bordt et al that the vaccine composition is in no way purified. While the Examiner indicates that Bordt et al is silent as to whether the virus is substantially free from cellular and serum components, and asserts that the product of Bordt et al "appears to be in a purified state", it is submitted that such is not the case. It is clear from Example I of Bordt et al that the ascorbic acid is added to virus fluid to effect the inactivation and this viral fluid is

not further processed in any way which would result in purification of the material.

While it is true that the Downing et al reference teaches a method of preparing respiratory syncytial virus by growing the RSV on HEp-2 cells, as indicated by the Examiner the specific aim of this study was:

"To determine if the viral matrix cellufine sulfate (MCS) interaction is indeed electrostatic and if the intact virus was required for binding and to determine an optimal elution scheme that maximized the separation of virus from cellular proteins and maximized the yield and concentration in the viral fractions".

The aim of the present application is purify virus to remove contaminating cellular and serum proteins to avoid the potential problem of non-viral proteins which enhance pulmonary pathology following exposure to wild-type virus. The objectives of the paper and the present application, therefore, are distinctly different. Downing et al do not teach inactivation of virus.

The McIntosh et al reference would not appear to add anything to Bordt et al in terms of the provision of a purified inactivated RS viral preparation substantially free from cellular and serum components, as required by applicant's claims. As the Examiner states, McIntosh et al teach that human RSV is the most important cause of viral lower respiratory tract disease in infants and children and that human RSV is a paramyxovirus. It is not seen of what relevance this observation has to the patentability of applicants claims.

The Examiner asserts that:

"It would have been obvious to one of ordinary skill in the art to inactivate human RSV for use as a vaccine because Bordt et al teach that paramyxoviruses may be inactivated with ascorbic acid and RSV is a paramyxovirus as taught by McIntosh."

However, there is absolutely no teaching in the combination of cited art which could lead the skilled person to the present invention as claimed in claims 1 to 4, 15 and 16. Bordt et al teaches only inactivation of non-purified bovine respiratory

syncytial virus using ascorbic acid. While Downing et al describes an RS virus purification process, there is no suggestion to inactivate that material.

Accordingly, it is submitted that claims 1 to 4, 15 and 16 are patentable over the cited prior art and hence the rejection thereof under 35 USC 103 as being unpatentable over Bordt et al in view of Downing et al and further in view of McIntosh et al, should be withdrawn.

The Examiner rejected claims 5 and 6 under 35 USC 103 as being unpatentable over Downing et al in view of Preston et al.

Claims 5 and 6 relate specifically to the method of making immunogenic composition. In such procedure, the RS virus is grown, harvested and purified under non-denaturing conditions to produce a purified virus substantially free from cellular and serum components. This purified virus then is inactivated with an inactivating agent as specified and then formulated as the immunogenic composition.

As discussed above, there is a prejudice in the art against inactivating respiratory syncytial virus. To date, no vaccine manufacturer or research laboratory has envisioned or suggested the use of inactivating agents for the production of a human RS virus vaccine. The applicants have found, however, that, if the virus first is purified and then inactivated and formulated as an immunogenic composition, then there is provided an effective RS viral composition which can protect the relevant animal model against the RS virus without causing disease potentiation.

As the Examiner correctly points out, the Downing et al reference does not teach inactivating the virus with  $\beta$ -propiolactone or indeed, any other inactivating agent. Indeed, as noted above, there is prejudice in the art against inactivating RS virus for the purposes of providing vaccine compositions in view of the problems associated with such inactivation using formalin. As discussed above, Downing describes a procedure for purifying the virus.

The purpose of the Preston study was to understand the immune response relating to the reduced resistance to subsequent RSV infections by in vitro studies aimed at inhibiting the proliferative T-cell response to inactivated RSV. The purpose of the  $\beta$ -propiolactone used in this study was to prepare inactivated RSV to be used only to stimulate the adult mononuclear cells for the purpose described above. The Preston et al reference contains no suggestion for inactivating virus which has been processed in accordance with applicant's recited process steps and indeed, there is no motivation whatsoever in either Downing et al or Preston et al to use the  $\beta$ -propiolactone inactivation described in Preston on the materials which are prepared by Downing. Indeed, as noted above, the art points away from any such activity.

Accordingly, it is submitted that claims 5 and 6 are patentable over the combination of Downing et al in view of Preston et al and accordingly, the rejection of claims 5 and 6 under 35 U.S.C. 103 as being unpatentable over this combination of art, should be withdrawn.

The Examiner rejected claims 5 and 9 under 35 U.S.C. 103 as being unpatentable over Downing et al in view of White et al. The teachings of Downing et al and the deficiencies thereof have already been discussed above. As the Examiner notes, Downing et al do not teach inactivating the virus with ascorbic acid. In addition, as already noted, there is no suggestion whatsoever in Downing to effect any such inactivation and, indeed, there is a prejudice in the art against doing so.

The White et al reference apparently is relied on for a teaching of inactivation of RSV by a treatment with ascorbic acid. The objective of the study reported by White et al was to determine the in vitro effect of ascorbic acid on viruses and to use the inactivated virus as a reagent in serologic assays, and not for the production of an inactivated RSV vaccine. The Examiner will note that applicants claims include the step of formulating the inactivated virus as an immunogenic composition.

As described in White et al, the infected cells are grown in roller bottles, scraped, disrupted by a freeze-thaw cycle and further clarified by centrifugation. This means of virus purification would not yield a viral preparation free of cellular contaminants. In addition, there would be no reason for a person skilled in the art to apply the teaching of White et al with respect to inactivation using ascorbic acid to the teachings of Downing et al in view of the clear prejudice in the art against inactivated preparations.

Accordingly, it is submitted that claims 5 and 9 are patentable over the combination of Downing et al in view of White et al and accordingly, the rejection of claims 5 and 9 under 35 U.S.C. 103 as being unpatentable over this combination of prior art should be withdrawn.

The Examiner rejected claims 5, 7 and 8 under 35 U.S.C. 103 as being unpatentable over Downing et al in view of Prince and Georgiades et al.

The Downing et al reference and its deficiencies have been discussed in detail above.

The Prince et al reference is apparently cited for a teaching of inactivation of plasma hepatitis virus by treatment with a non-ionic detergent which may be n-octyl- $\beta$ -D-glycopyranoside. The Georgiades et al reference apparently is relied on for a teaching of inactivation of contaminating viruses in interferon  $\alpha$  solutions by treatment with non-ionic detergents.

The Prince et al reference relates to the use of non-ionic detergents to sterilize blood plasma so that it is free of active hepatitis virus. There are distinct differences between the hepatitis virus and RSV. Hepatitis B is a DNA virus belonging to the hepadnaviridae family of viruses, while RSV is a negative strand RNA virus belonging to the paramyxoviridae virus family. The conditions found suitable for inactivating viruses belonging to the hepadnaviridae family of viruses may not be suitable for viruses belonging to the paramyxoviridae family. In the Prince et al reference, it is recommended that a combination

of a non-ionic detergent, alcohol or ether or a mixture of both be used to inactivate hepatitis viruses during plasma processing. Detergent alone is used in the present application to inactivate RSV.

The Georgiades et al reference deals with the process for the purification of interferon  $\alpha$  and to a method of enhancing the overall recovery of interferon  $\alpha$ . The purpose of using the detergent in the reference was to eliminate virus contamination and not to produce killed viral vaccines.

As previously noted, the art is prejudiced against using inactivated RS virus for vaccine use and there is no motivation in the cited prior art to inactivate RS virus using non-ionic detergents, in particular, glucopyranosides. Accordingly, it is submitted that claims 5, 7 and 8 are patentable over the combination of Downing et al in view of Prince and Georgiades et al and hence, the rejection of those claims under 35 U.S.C. 103 as unpatentable over this combination of prior art should be withdrawn.

The Examiner rejected claims 5, 10, 12 and 13 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al.

The Ewasyshyn et al reference describes the production of purified surface glycoproteins of RSV and PIV-3. The only similarity or relevance to the present invention is that both the present invention and Ewasyshyn et al describe growing and harvesting RS virus. Thereafter, the processes diverge significantly. The present invention further processes the harvested whole virus, while Ewasyshyn et al then solubilize and isolate glycoproteins from the harvested virus. The Ewasyshyn et al reference does not teach inactivation of virus, as noted by the Examiner. This is because the Ewasyshyn et al procedure extracts the surface glycoproteins from the virus and is concerned solely with processing that extracted material.

The Examiner indicates that the Mbiguino et al reference is relied on for a teaching of purification of RSV

under non-denaturing conditions using a sucrose gradient. The protocol described by Mbiguino et al is cumbersome and time-consuming and, in any event, unrelated to vaccine development. The rationale employed by Mbiguino et al for producing a highly purified preparation of RSV was not to eliminate contaminating cellular and serum proteins which may contribute to enhanced pulmonary pathology following live virus challenge, but rather was to compare different gradients, namely sucrose, percol, renografin and metrizamide, for purifying RSV.

It is clear, therefore, that claims 5, 10, 12 and 13 are patentable over this combination of prior art since whatever modification the Examiner proposes to make to the Ewasyshyn et al procedure, that procedure is concerned with producing different materials from the product of the present invention and hence, the combination of prior art is irrelevant to the claimed invention.

Accordingly, it is submitted that claims 5, 10, 12 and 13 are not open to rejection under 35 U.S.C. 103 as being unpatentable over the combination of Ewasyshyn et al and Mbiguino et al and hence, the rejection should be withdrawn.

The Examiner rejected claim 11 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al as applied to claims 5, 10, 12 and 13 and further in view of McIntosh et al and Paradiso et al.

The deficiencies of the teachings of Ewasyshyn et al and Mbiguino et al have been discussed above and do not require further discussion. Claim 11 is concerned specifically with growing the RS virus on VERO cells and as the Examiner points out, McIntosh and Paradiso both describe the use of VERO cells for growing RS virus. Accordingly, the McIntosh et al and Paradiso et al references would not appear to remedy the defects of the basic combination of Ewasyshyn et al and Mbiguino et al as discussed above.

Having regard to those defects, it is submitted that claim 11 is not open to rejection under 35 U.S.C. 103 as being unpatentable over the combination of Ewasyshyn et al, Mbiguino

et al, McIntosh et al and Paradiso et al and hence, the rejection should be withdrawn.

The Examiner rejected claim 14 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler. The disclosures of the Ewasyshyn et al and Downing et al references have previously been discussed. The Kuchler reference apparently is relied on for a general teaching of the steps involved in purification of viruses generally describing the use of the chromatographic and ion-exchange resins, molecular sieving on gel filtration columns, countercurrent distribution or by gradient centrifugation. This reference, therefore, is nothing but a general teaching of common purification operations. Claim 14 defines a specific combination of purification steps which, it is submitted, is nowhere disclosed or suggested in the Kuchler reference.

Having regard to the deficiencies of the Ewasyshyn et al and Downing et al references as outlined above, and having regard to the lack of specificity in the Kuchler reference with respect to the process steps employed in claim 14, it is submitted that claim 14 is clearly patentably distinguished from the prior art that the Examiner relies on. Accordingly, it is submitted that the rejection of claim 14 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler, should be withdrawn.

The above discussion of the prior art is consistent with the applicants discussion of the cited prior art in the Amendment of April 4, 1996. The Examiner indicated in the Office Action that applicants arguments had been considered but were not deemed persuasive.

The Examiner comments:

"Several references have been cited above which teach such kinds of steps."

The Examiner is referring to applicants steps of purifying grown virus, and the inactivating and formulating the virus. While individual ones of the steps may be described in the art, they have not been used in combination in the order employed by the applicants and there is a clear lack of

motivation in the art to combine the steps, since inactivation of virus is not considered to be a viable route to obtaining an effective immunogenic composition which can provide protection in the absence of disease potentiation.

The Examiner further states:

".... newly added references by Murphey-Corb et al teach that 'using a macaque model, a formalin-inactivated whole-virus vaccine and two subunit vaccines were tested for efficacy against SIV infection. Immunization with formalin-inactivated SIV protected 8 of 9 monkeys against viral infection following challenge with 10 animal infection doses. A glycoprotein prep. of detergent-disrupted virions prevented infection and disease in only 2 of 4 monkeys'. Thus, it is clear that there is prior art which teaches use of inactivated virus as vaccine to treat infection."

While this comment correctly describes the Murphey-Corb reference, it is not seen in what manner immunization of monkeys with inactivated SIV virus is in any way relevant to applicants RS viral preparation and method of production of the same. Applicants invention is concerned with a specific virus, namely respiratory syncytial virus, which is in no manner related to the retrovirus SIV. As far as applicants are aware, disease potentiation is not a problem with SIV.

The Examiner indicates that claims 1 to 16 are rejected under 35 USC 103 as being unpatentable "over above cited references" and further in view of Murphey-Corb et al. The Examiner does not identify which particular ones of the "above cited references" are combined with Murphey-Corb et al. Nevertheless, the distinctions of claims 1 to 16 over the specific combinations of prior art cited against them are set forth in detail above. It is submitted that the Murphey-Corb reference in no manner remedies the defects of the combinations of reference applied against the respective claims.

Accordingly, it is submitted that claims 1 to 16 are patentable over the applied art and that the rejection of claims 1 to 16 under 35 USC 103 as being unpatentable over "above cited references" in view of Murphey-Corb et al should be withdrawn.

It is believed that this application now is in condition for allowance, and early and favorable consideration and allowance are respectfully solicited.

Respectfully submitted,

  
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